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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/567,275	05/09/2007	M. Ian Phillips	USF.199TCXZ1	9704

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EXAMINER	
BERTOGLIO, VALARIE E	
ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
10/26/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

euspto@slspatents.com

Office Action Summary	Application No.	Applicant(s)	
	10/567,275	PHILLIPS ET AL.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08/16/10*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-26 and 29-46* is/are pending in the application.

4a) Of the above claim(s) *30 and 31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-26,29 and 32-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 February 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Application has been transferred to Examiner Valarie Bertoglio, AU 1632.

Applicant's response dated 08/16/2010 is acknowledged and entered.

Election/Restrictions

Applicants' election of Group III (claims 17-26), drawn to a method of targeting a stem cell to a target tissue in a subject by *ex vivo* cell therapy is noted. Claims currently encompass non-elected embodiments and such subject matter should be removed from the claims prior to allowance.

Elected species are heart as a target tissue, viral vectors, MLC-2v as the tissue-specific promoter, and hSDF-1 as the stem cell-attracting chemokine.

Claim 17 is amended. Claims 1-16 and 27-28 are cancelled. Claims 29-46 are added.

Newly submitted claims 30-31 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claims 30 and 31 fail to read on the elected species of promoter (MLC-2v), which is a heart-specific promoter.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 30-31 withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-26,29 and 32-46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The instant invention is drawn to a method to recruit stem cells, either endogenous or exogenously administered, to a site in the body where those stem cells are needed to replenish a healthy supply of differentiated cell types. The invention is drawn to carrying out such a method using a vector system with elements that result in expression of a stem cell-attracting chemokine in an area of need.

The claims encompass both in vivo and ex vivo gene therapy. However, Applicant has elected ex vivo gene therapy (i.e. cell therapy) for examination. The specification contemplates ex vivo gene therapy, or cell therapy, at page 16 of the specification, where it teaches introducing the vector system of

the invention into stem cells followed by transplantation of the cells back into the host. The specification teaches that any of numerous administration routes can be used to deliver the cells, including jugular vein, tongue vein, IP and IV injection.

The specification provides a working example that teaches gene therapy, or direct injection of the plasmid vectors into the host. In example 2, the target tissue is the heart and the plasmids were delivered by intracardial injection, right to the site of need. The specification does not teach, by way of example, the elected invention of ex vivo gene therapy. The specification does not provide guidance regarding how cells carrying the plasmid constructs will reach the desired tissue location and does not teach what cell types can be used to deliver and express the plasmid constructs in each desired location. Thus, for example, the claims encompass IV injection of epithelial cells comprising the polynucleotides of the claims, with the goal of targeting stem cells to the heart. The specification does not support that any cell type will, itself, home to the desired location, and express the chemokine that is intended to attract stem cells to that location. After all, the object of the invention is to aid in the homing of cells to the tissue of interest.

It is noted that the claims are not limited to the elected invention or species. Applicant elected used on the MLC-2v promoter, which is active in heart cells, not any cell type encompassed by the claims. Thus, in light of the election of the MCL-2v promoter, claims should be limited to use of cell types in which the elected promoter would be active. Without such a limitation, the claims are not enabled because the nucleic acid construct of the invention will not be expressed in any cell type in which the MLC2v promoter is not active.

Christoforou and Gearhart (**Progress in Cardiovascular Diseases** Volume 49, Issue 6, May-June 2007, Pages 396-413) discuss the state of the art relating to transplant of stem cells into the heart for therapeutic value. Successful attempts at cell therapy in the heart are limited with regard to the cell types used as well as the delivery method. In general, cardiomyocytes or multipotent stem cells with the

capacity to differentiate into cardiac cells are used and the cells are transplanted directly into the heart. Difficulties associated with use of stem cells in the inability to obtain an effective quantity of a desired stem cell type from an individual. Use of ES cells to overcome this difficulty poses problems of immune compatibility as well as undesired effects of the transplanted cells (see page 409).

Other unpredictable factors complicate cellular transplantation, as well. Inverardi et al. (**Transplant Biology**, 1996) review the state of the art of cell transplantation and discuss various factors that affect successful cellular transplantation, such as problems of cell isolation and purification, cellular environment, the immune response to transplanted cells, as well as the preservation of cells used in cellular transplantation (see pp. 679-681). Inverardi et al. further review various clinical applications for cellular transplantation, each with varying results (see pp. 681-684). Inverardi et al. discuss the genetic engineering of cells to be used in cellular transplantation, and discuss the limitations of currently available gene delivery systems (see p. 685). These unpredictabilities are further supported by Verma et al, (Nature, 389:239-242, 1997) who teaches that transgene expression can abruptly cease in transplanted, recombinant cells. This transcriptional shut-off has even been observed in mice lacking a functional immune system (nude mice), and it cannot be due to cell loss or gene deletion because the transplanted cells can be recovered." (See paragraph bridging left and middle columns of page 240). The specification fails to teach how to overcome the aforementioned unpredictabilities associated with the ex vivo gene therapy art.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 44 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 44 is unclear as it recites "coadministering to the target tissue stem cells and an agent that causes the stem cells to migrate to the target tissue". It is not clear if the cells and the agent are both administered to the target tissue as the agent that causes migration of the stem cells to the target is not needed if the stem cells are administered to the target. In light of this rationale, it is not clear whether the agent of claim 44 is different from the vector system of claim 17 and whether the stem cells attracted by the agent of claim 44 are the same as those recited in claim 44. Alternatively, the administered cells of claim 44 may provide the agent, also recited in claim 44. Clarification is necessary.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 17-22 and 24-26 remain rejected and newly added claims 32-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Petersen et al. (U.S. Patent Publication No.: 2002/0094327; effective filing date: Nov. 5, 2000), in view of Phillips et al. (Hypertension 39(part 2):651-655, 2002), and further in view of Tang et al. (Hypertension, 39(part 2):695-698, 2002). The rejection is maintained for reasons of record set forth at pages 3-6 of the office action dated 07/14/2009. The limitations of claims 32-46 are set forth in the rejection as outlined in the action of 04/14/2009. Applicant's arguments have been fully considered and are not persuasive.

Applicant argues that the references cited were all published about the same time and that the lack of combining the references to yield a single prior art publication teaching the claimed invention is evidence that it was not obvious to combine said cited references. The lack of a single reference teaching the claimed invention doesn't exist doesn't negate the obviousness of combining the references. If such was a requirement, then obviousness would not be an issue of patentability.

Applicants also assert that the cited references do not provide a reasonable expectation of success. Applicants argue that it took considerable experimentation to conceive and develop the claimed invention and that this experimentation was ongoing between the publications cited and the filing of the instant application. In response, the combination of the references merely requires the substitution of therapeutic genes with the SDF-1 chemokine gene. The claims merely require the targeting of a stem cell to a target tissue using SDF-1. The art showed high levels of expression of a gene of interest in the vector system of Phillips and of Tang. It was known in the art that SDF-1 attracts stem cells. Thus, it is reasonable to expect that the vector system of Phillips and of Tang would result in attraction of a stem cell to any tissue wherein it is used.

Applicants assert that an SDF-1 gene could fit in the vector system of Phillips and of Tang. In response, the amount of experimentation required to place the SDF-1 gene into the vector system of Phillips and of Tang is well within the skill of the ordinary artisan. There is no evidence or rationale on

the record suggesting that the SDF-1 gene would not work in the claimed system. Furthermore, the state of the art of nucleic acid subcloning is highly developed and has been for decades. Finally, Applicant argues that the ability of SDF-1 to attract cardiac stem cells was not known in the art at the time of the present invention and is particularly advantageous for treatment of cardiovascular pathologies. In response, the claims fail to require the attraction of *cardiac* stem cells and the claims fail to require any treatment effect. Claim 1 merely recites, in the preamble, "A method of targeting a stem cell to a target tissue". The art renders it obvious to carry out the claimed active method steps. Any effect from such method steps would be inherent to the method.

The examiner recognizes that obviousness may be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988), *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992), and *KSR International Co. v. Teleflex, Inc.*, 550 U.S. 398, 82 USPQ2d 1385 (2007).

Claims 17 and 23 remain rejected and claim 44 is rejected under 35 U.S.C. 103(a) as being unpatentable over Petersen et al. (U.S. Patent Publication No.: 2002/0094327; effective filing date: Nov. 5, 2000), in view of Phillips et al. (Hypertension 39(part 2):651-655, 2002), and Tang et al. (Hypertension, 39(part 2):695-698, 2002), as applied to claims above, and further in view of Kovesdi (USPGPUB 2003/0027751). The rejection is maintained for reasons of record set forth at pages 6-7 of the office action dated 07/14/2009. Applicant's arguments have been fully considered and are not persuasive.

Applicant's arguments regarding this rejection were combined with those reiterated and addressed above. The rejection is maintained, therefore, for reasons set forth above.

Claims 17-22,24-26, 29-43,45-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Petersen et al. (U.S. Patent Publication No.: 2002/0094327; effective filing date: Nov. 5, 2000), in view of Tang et al. (Methods, 28:259-266, 2002; referred to as Tang2).

The claims encompass a method of targeting a stem cell to the heart of a subject by *ex vivo* cell therapy, the method comprising administering to the heart tissue a composition comprising: (a) a first polynucleotide comprising: (1) a gene switch/biosensor comprising a nucleic acid sequence encoding a physiological stimulus-sensitive chimeric transactivator, and (2) an operatively linked MLC-2v cardiac promoter; and (b) a second polynucleotide comprising a nucleic acid sequence encoding the stem cell-attracting chemokine hSDF-1.

Petersen et al. describe a method of modulating the targeting of pluripotent stem cells to a target tissue of a mammalian subject by increasing the concentration of SDF-1 alpha protein in the target tissue (Abstract). The mammalian subjects include humans and non-humans (paragraph [0063], limitation of claim 17), and the target tissue can be the heart (paragraph [0063], p. 8, limitation of claim 19). Peterson states that the mammalian SDF-1 alpha genes, including the human gene are known (paragraph [0030], and may be used as part of a heterologous DNA under the control of a tissue-specific promoter (paragraph [0086]), using AAV-based vectors (paragraph [0084], limitation of claim 18). *Ex vivo* gene transfer of the SDF-1 alpha nucleic acid under the control of a tissue specific promoter to host cells , followed by delivery of the transfected cells to the host is described in paragraph [0104], p. 13 (limitation of claim 20). In Example 2, Petersen et al. describe SDF-1 alpha expression in a model of tissue injury (p. 14, limitation of claim 25). The authors additionally describe using agents that increase the transcription or translation of a gene encoding SDF-1 alpha in a target tissue, that may also be used in the invention (paragraph [0068], p. 9; limitation of claim 24), or using agonists (claim 1, p. 14), or G-CSF to increase the number of stem cells in the peripheral blood (paragraph [0009], p. 1).

While Petersen et al. do not describe expressing their tissue specific SDF-1 alpha gene expressed

via a transactivator comprising a GAL4 DBD, an ODD, and a p65 AD wherein the second nucleic acid comprises a UAS wherein the transactivator binds the UAS in response to hypoxia, such was taught by Tang2.

Tang2 taught a double vector model comprising a first nucleic acid encoding an oxygen-sensitive transactivator (GAL4/ODD/p65AD) as claimed. The second nucleic acid includes UAS linked to a cardioprotective transgene.

It would have been obvious at the time of filing to substitute the cardioprotective transgene of Tang2 with the SDF stem cell chemoattractant of Petersen to express exogenous SDF in the heart. One would have been motivate to make such a substitution as Tang2 taught a highly specific control of gene expression in response to hypoxic events using the vector system to express a transgene in the heart only in response to hypoxia. One of ordinary skill in the art would have been afforded a reasonable expectation of success in carrying out the combination as the vector system was already show to be effective and the technology to exchange the transgene of interest was highly developed such that one could readily make the substitution.

Claims 17,23 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Petersen et al. (U.S. Patent Publication No.: 2002/0094327; effective filing date: Nov. 5, 2000), in view in view of Tang et al. (Methods, 28:259-266, 2002; referred to as Tang2), as applied to claims above, and further in view of Kovesdi (USPGPUB 2003/0027751).

The teachings of Petersen and Tang2 are set forth above. Neither reference teaches coadministration of stem cells.

Kovesdi et al. describe vectors that include polynucleotides encoding VEGF fusion proteins that promote angiogenesis and wound healing (Abstract). Kovesdi et al. disclose that the vector may be

administered to any cardiac tissue of the heart (paragraph [0161], and additionally co-administered with factors such as GM-CSF, in association with the administration of stem cells (paragraph [0171], thus curing the deficiency in Petersen et al.

As the disclosure of Petersen et al., and Kovesdi et al. are directed to gene delivery to the heart of a subject and further recruitment of stem cells to the target tissue, it would have been *prima facie* obvious for a person of ordinary skill in the art, to combine their respective teachings and to co-administer stem cells with the vector of Petersen as instantly claimed, with a reasonable expectation of success, at the time of the instant invention. A person of ordinary skill in the art would be motivated to co-administer stem cells with a therapeutic polynucleotide to the heart of a subject, because such was specifically taught by Kovesdi et al. and would result in increased wound healing and tissue repair.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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